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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20040217

Application Number: 09/759,345
Filing Date: January 16, 2001
Appellant(s): ROBINSON, DOUGLAS H.

Joyce von Natzmer
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11-17-2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is deficient because Applicant states on page 2 of the instant brief that the claimed invention is drawn to methods of producing altered cells that have all the morphological characteristics of bacteria (and hence would be classified as bacteria by the objective observer) from a culture of eukaryotic cells wherein said altered cells contain one or more eukaryotic or viral genes. The instant claims are drawn to methods of producing bacteria containing one or more eukaryotic or viral genes from eukaryotic cells not

cells with all the morphological characteristics of bacteria. Moreover, classification of bacteria is not predicated solely on morphological characteristics alone. Classification is based on a multitude of factors including genomic characteristics, biochemical processes in addition to morphological characteristics.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: Applicant states on page 9 that "the fifth issue is whether or not claims 24-29 meet the written description requirement of 35 U.S.C. 112, **second** paragraph". In actuality, the written description rejection of claims 24-29 was made under 35 U.S.C. 112, **first** paragraph.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-29 are grouped together with regard to the issues utility, enablement and indefiniteness (based on the lack of correspondence in scope between the claims and the specification).

Appellant's brief includes a statement that claims 1-23, 26 and 28 do not stand or fall together with 24-25, 27 and 29 with regard to the issues of written description and indefiniteness (based on the use of the terms "derived", "evolved", "pleiomorphic" and "morphology that is neither prokaryotic or eukaryotic") but does not provide reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

First Issue

35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-29 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility, as the disclosed invention is inoperative.

The claims are drawn to a method for **producing a bacterium** that contains a eukaryotic and/or viral gene, which comprises culturing virally infected eukaryotic cells under low oxygen conditions to produce a bacterium containing a eukaryotic and/or viral gene. The specification at page 9 indicates that the present invention provides a process for producing a bacteria containing at least one eukaryotic gene. The specification at page 9 further states "the process of the present invention, sometimes called *de novo* speciation, can be divided into the following stages:

(I) Culturing virally-infected eukaryotic cells under low oxygen conditions to **produce a bacterium** containing a eukaryotic and/or viral gene; and

(II) Selecting and replicating at least one such bacterium."

Accordingly, the claims and the specification call for a method for producing a bacterium containing a eukaryotic and/or viral gene, which comprises culturing virally-infected eukaryotic cells under low oxygen conditions to produce a bacterium containing a eukaryotic and/or viral gene whereby neither the bacterium nor the bacterial genome is introduced. Barron's Law Dictionary 3rd Edition defines *"de novo "* as "new, young, fresh; renewed, revived..." and Webster's II New Riverside Dictionary defines "speciation" as "the evolutionary process by which new species are formed." Therefore, Applicant is calling for the *de novo* "creation" of a new species and/or the "creation of a life form", i.e., the bacterium, from eukaryotes without the introduction of bacterial genes or the bacteria themselves. However, current knowledge of scientific principles maintains that prokaryotes and eukaryotes constitute separate and distinct life forms having many differences in structure and function. The most striking difference pertains to the presence or absence of a nucleus. That the only recognized process in the art for the acquisition of new traits is mutation is well settled. Moreover, the process of the acquisition of new traits is a slow process that requires so many changes that more than anaerobic cultivation for a few hours or even a few years is necessary. To the best of scientific knowledge, the evolution of first one-celled and then many-celled eukaryotes from one-celled prokaryotes is believed to have taken several million years and not a few hours or days. Likewise, it appears that Applicant is calling for the "spontaneous" production of a new bacterium without the introduction of the bacteria or the bacterial genome. It should be remembered that Louis Pasteur effectively disproved the principles of spontaneous generation at the end of the last century in historical experiments. Therefore, the specification fails to show a clear correlation between culturing retrovirally infected animal cells in the amount of oxygen given and the "creation" (i.e., the production) of a new species of bacteria.

Second Issue

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The invention appears to employ novel strains of Staphylococcus and Micrococcus. It's not clear if the written description is sufficiently repeatable to avoid the need for a deposit. Further it is unclear if the starting materials were readily available to the public at the time of the invention.

It appears that a deposit was made in this application as filed (page 8). However, it is not clear if the deposit meets all of the requirements of the criteria set forth in 37 CFR 1.801-1.809. Applicant or Applicant's representative may provide assurance of compliance with the requirements or 35 U.S.C. § 112, first paragraph. If the deposit was made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants or assignees, or a statement by an attorney of record over his or her signature and registration number, stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository, is required. This requirement is necessary when a deposit is made under provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and address of the depository, amendment of the claims to refer to the accession number, is required, in addition, claims reciting the deposited material must be amended to include the depository accession number of the deposited material.

Furthermore, unless the deposit was made at or before the time of filing, a declaration filed under 37 C.F.R. 1.132 is necessary to construct a chain of custody. The declaration, executed by a person in a position to know, should identify the deposited the bacteria by the depository accession number, establish that the bacteria is the same as that described in the specification, and establish that the deposited bacteria were in applicants' possession at the time of filing.

Third Issue

Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for isolating a bacterium comprising aseptically culturing retrovirally transformed human capillary microvascular endothelial cells (ATCC CRL 11655); subjecting said culture to an anaerobic culturing phase wherein said culture is exposed to oxygen conditions corresponding to an atmosphere containing of about 0 to 2% v/v oxygen for a period of between 18 and 24 hours; exposing said culture to oxygen conditions corresponding to an atmosphere containing greater than 2% v/v oxygen; subjecting said culture to an additional anaerobic culturing phase wherein said culture is exposed to oxygen conditions corresponding to an atmosphere containing of about 0 to 2% v/v oxygen for a period of between 18 and 24 hours; subjecting said culture to an additional aerobic culturing phase under aseptic culturing conditions and corresponding to an atmosphere containing greater than about 2% v/v oxygen; isolating a bacterium from the culture (either *Staphylococcus aureus* ATCC 55589, *Staphylococcus capitis* ATCC 55590, *Staphylococcus hemolyticus* ATCC 55592, *Staphylococcus epidermidis* ATTC 55591 or *Micrococcm luteus* ATCC 55588), does not reasonably provide enablement for methods for **producing** a bacterium that contains a eukaryotic and/or viral gene comprising

culturing virally-infected eukaryotic cells under low oxygen conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. .

It does not appear that the claimed method would be suitable for the production of bacteria from any and all eukaryotic cells. From the record of the written disclosure specific bacteria were obtained by the cultivation of the specific cell lines in specific media. In view of the specific nutritional requirements of different types of "cell cultures" and of different bacteria, there is no reasonable expectation that any and all types of bacteria may be "produced" or even isolated from any and all cell cultures by the procedure claimed. For example, any anaerobic bacteria would be destroyed upon exposure to aerobic conditions. In addition, the claims lack specific method steps for the recovery of the bacteria. Thus, it is unclear that the claimed method would be suitable for the recovery of any and all bacteria, a few of which may be present, but not detectable by certain means. Moreover, one of ordinary skill in the art would not reasonably expect any and all possible viral infected eukaryotic cell cultures to harbor or to be contaminated by bacteria, especially if stringent aseptic technique is used. In this respect, it is apparent that only very specific sources of cell cultures would be suitable for the claimed invention. However, the specification provides insufficient guidance for one skilled in the art to obtain such cell cultures. In addition, it is unclear what precautions were taken in the instant case to assure that the bacteria harvested are not incidental contaminants inadvertently introduced into the cell culture. Moreover, it is well known in the art that the strains of bacteria that were recovered after the claimed method are common cell culture contaminants. Thus, there is no clear correlation between the instant method of culturing and the production of **new strains of bacteria**.

It is also apparent that the claimed method is unpredictable and would appear to depend on the type of cell cultured and the type of virus employed. It is unclear how the cell culture is chosen to have a reasonable degree of certainty that bacteria as required can be "produced", in the absence of positive steps to modify existing bacteria and to assure the survival of the cell culture for a time period. What step actually produces the bacterium? Is it sufficient for any bacterium to be grown in any virally infected eukaryotic cell in order to acquire both eukaryotic and viral genes? Accordingly, in view of the lack of guidance, the claims as written constitute nothing more than an invitation to experiment.

The present invention would also require undue experimentation to practice in view of the unpredictable completion of the culturing steps. The specification indicates that the cultured cells under anaerobic conditions results in the death of the eukaryotic cells. However, the claims include no such limitation, accordingly, it is unclear if the eukaryotic cells are to be living or dead at this point. Likewise, the specification indicates that culturing under low oxygen conditions results in the production of the bacterium. However, what actual step leads to the production of the bacterium? Where are the genetic elements necessary for this event to occur (i.e., what is the origin of the bacteria)? While it is true that bacteria are a frequent contaminant of a cell culture, it is not apparent that the purpose of the present invention is to recover contaminants. Furthermore, how long is one of skill in the art to culture the virally infected eukaryotic cells. On the other hand, how long does one of skill in the art have to culture the cells anaerobically in order to "produce" a bacterium containing a eukaryotic and/or viral gene? Likewise, which eukaryotic cells should one use, and what virus should be employed?

Additionally, it is unclear how one of skill in the art would determine and assure that the actual viral and/or eukaryotic genes are indeed intact genes picked up rather than random fragments thereof. The cell line of

the specification uses retrovirally-infected cells. However, by convention, retroviral genes have been found to be ubiquitous in all types of different organisms, such that virtually any cell culture would reasonably be expected to have at least pieces of DNA from these viruses. In addition, it is well known in the art that many animal species harbor endogenous retroviral genes. However, it is unclear how one skilled in the art would determine that the cell culture has these "genes" without undue experimentation. Regarding the genes or fragments that are to be present in the bacteria, it is unclear whether such pieces are to be stably incorporated into the genome and that proteins will be expressed by them. For DNA to integrate, homologous recombination is needed, such that the respective sequences must already be present in the bacteria. Therefore, it is unclear whether a stable product is produced.

In view of the lack of guidance provided by the disclosure, the limited number of working examples, the state of the art, the breadth of the claims, and the unpredictably nature of the invention, it would take an undue amount of experimentation to practice the claimed invention.

Fourth Issue

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 15 are rendered vague and indefinite by the use of the language "under low oxygen conditions...". The metes and bounds of this claim terminology are unclear. What is a low oxygen condition? How low should the oxygen content be?

Claims 2, 3, and 15 are vague and indefinite and confusing. These claims recite, "subjecting the cells to an aerobic culturing step", yet they depend upon claims that require culturing under low oxygen conditions. Accordingly, such claims are contradictory

Claims 1-29 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims 1-29 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in Paper No. 7 and 8 filed 6-24-2000. In that paper, applicant has stated "any eukaryotic genes present in bacteria produced by the claimed methods would be intact, stable and integrated in the genome, because that would be their condition prior to the performance of the claimed methods", and this statement indicates that the invention is different from what is defined in the claim(s) because said statement indicates that the genome of the "produced" bacteria is eukaryotic in nature suggesting that the claimed method induces a "de-evolution" of the eukaryotic cell. The instant claims are drawn to methods of producing a bacterium that contains a single eukaryotic gene not a bacterium that has the phenotype of a prokaryote and the genotype of a eukaryote.

Claims 24 and 25 are rendered vague and indefinite by the use of the term "derived". It is unclear what is meant by said term. What steps are required for this "derivation"? What are the starting materials? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 24 and 25 are rendered vague and indefinite by the use of the term "evolved". It is unclear what is meant by said term. All genes in a given eukaryotic genome have "evolved" from an ancestral genome since evolution is an inherent trait of all genomes.

Claims 24 and 25 are rendered vague and indefinite by the use of the term "pleiomorphic cell". It is unclear what is meant by said term. It is unclear how the cell of the instant claim differs from any other cell

since all cells are pleiomorphic by nature. As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 27 and 29 are rendered vague and indefinite by the use of the phrase "morphology that is neither prokaryotic nor eukaryotic". It is unclear what is meant by said phrase since "eukaryotic" and "prokaryotic" are taxonomical classifications and not morphology types. Further, if eukaryotic and prokaryotic morphologies are excluded, it is not clear what morphology is included within the claimed limitations.

Fifth Issue

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 24 and 25 recite the limitation that the claimed cell is not a transgenic cell. This limitation is not supported by the specification.

(11) Response to Argument

Issue One

Applicant argues:

1. The specification shows by provision of detailed protocols and actual data that the claimed invention is operative.

2. Applicant has submitted a detailed report (accompanied by declarations) that demonstrates through independent corroboration of the results reported in the specification, that the claimed methods work.

3. The claimed invention is a method that allows one to take cultured retrovirally-infected eukaryotic cells (uncontaminated with bacteria), subject them to a series of specific culturing conditions and obtain a culture of cells that morphologically can only be described as bacteria wherein said cells contain intact eukaryotic and/or viral genes (see page 8-9 of the appeal brief).

4. One of ordinary skill in the art would clearly understand that the applicant is claiming a process that results in the alteration of a life form which is conceptually the same as the results achieved by DNA transformation of a plant cell, creation of a transgenic mouse, etc.

5. It is improper to simply conclude that a particular utility is flawed, particularly in the face of contrary evidence.

6. The examiner never addresses the fact that the evidence specification and the submitted Declarations indisputably demonstrate the operability of the claimed invention.

7. The "Final Report" referred to in the Steuer Declaration "provides supporting evidence for the hypothesis of *de novo* evolution of bacteria from eukaryotic cells" and that "environmental contamination is unlikely".

8. The "Final Report" conclusively shows that microorganisms having all the morphological characteristics of bacteria were **isolated** from the culture at the end of each of four experimental runs.

9. The "Final Report" contains a Quality Assurance statement showing that FDA and EPA Good Laboratory Practices where followed. Hence, "environmental contamination is unlikely", thus overcoming the Patent Office's position that the results were attributable to contamination.

Examiner Rebuts:

Contrary to Applicant's assertion to the contrary (Points 1 and 2), neither the specification nor the subsequent Declarations demonstrate that the claimed invention is operable. Neither demonstrates the operability of the claimed methods of **producing** bacteria that contains a eukaryotic and/or viral gene, which comprises culturing virally-infected eukaryotic cells under low oxygen conditions. It should be noted that, Applicant's assertion that the instant invention is drawn to a "method that allows one to take cultured retrovirally-infected eukaryotic cells (uncontaminated with bacteria), subject them to a series of specific culturing conditions and obtain a culture of cells that morphologically can only be described as bacteria wherein said cells contain intact eukaryotic and/or viral genes" (Point 3) is inaccurate. All claims are drawn to the methods of producing bacteria containing a eukaryotic and/or viral gene not "cells that morphologically can only be described as bacteria wherein said cells contain intact eukaryotic and/or viral genes". Additionally, only claims 6-7, 11-12 and 18 recites the limitation that the eukaryotic cell has to be retrovirally infected. Furthermore, no claim recites the limitation that the eukaryotic or viral gene contained within the "produced" bacteria must be "intact". Finally, no claim recites the limitation that the eukaryotic cultures need to be "uncontaminated by bacteria".

Applicant argues that the methods of the instant invention constitute an alteration of a life form not the "generation" of a life form. However, Applicant himself refers to the instant methods as *de novo* speciation (see Robinson Declaration and page 9 of the specification). Barron's Law Dictionary 3rd Edition defines *"de novo"* as "new, young, fresh; renewed, revived..." and Webster's II New Riverside Dictionary defines "speciation" as "the evolutionary process by which **new** species are formed." Therefore, contrary to his assertion, Applicant is calling for the *de novo* "creation" of a new species and/or the "creation of a life form", i.e., the bacterium, from eukaryotes without the introduction of bacterial genes or the bacteria themselves (which differs drastically in both theory and practice with standard recombinatory techniques). However, the only bacteria isolated using the instant methods were of the species *Bacillus lichenformis* (see page 9 of the Final Report and page 9 of the specification). This is in direct contradiction to Applicant's stated goals of the instant invention.

Contrary to Applicant's assertion, none of the evidence presented demonstrate the operability of the claimed invention. While it is true that Dr. Steuer made the statement that the "isolation of bacteria from eukaryotic cells subjected to alternating anaerobic/aerobic conditions provides supporting evidence for the hypothesis of *de novo* evolution of bacteria from eukaryotic cells", said statement does not constitute evidence that the instant invention is operable. If anything, said report merely demonstrates that the instant invention can be used to "isolate" *Bacillus lichenformis*. The report provides neither evidence demonstrating that the instant methods resulted in the production of a new bacterial species nor any evidence demonstrating that the isolated *Bacillus lichenformis* contained any viral or eukaryotic genes or any evidence that said isolated bacteria differs in any way from "normal" *Bacillus lichenformis*. It should be noted that throughout the "Final Report", Dr. Steuer states that the methods of the instant invention "resulted in the **isolation** of bacteria..." (See page 1 of Final Report for example). Consequently, for the reasons set forth above, the specification fails to show a clear

correlation between culturing virally (retrovirally) infected eukaryotic cells in the amount of oxygen given and the "creation" (i.e., the production) of a new species of bacteria.

It should also be noted that Applicant incorrectly asserted that all four experimental runs disclosed in the "Final Report" resulted in the production of microorganisms having all the morphological characteristics of bacteria. In fact only 2 runs resulted in the isolation of any bacteria (*Bacillus lichenformis).*

Second Issue

Applicant argues:

1. The requirement, to the extent it is required has already been met. Samples of cells obtained in the work reported in the Examples have been deposited with ATCC in compliance with the Budapest Treaty.

2. Eukaryotic cell lines used as starting materials are all publicly available.

Examiner rebuts:

Not all starting materials are publicly available. The porcine cerebral microvascular endothelial cells are listed as being held by Applicant. Moreover, Applicant has not articulated that the deposited materials encompassed by claims 24-29 have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository, is required.

Third Issue

Applicant argues:

1. The examiner improperly ignores evidence of record that demonstrates that the claimed method functions as claimed to produce bacteria containing eukaryotic and/or viral genes from an aseptic culture of retrovirally-infected eukaryotic cells.

2. The examiner insists that the bacteria produced are the result of contamination of the starting cultures.

3. The examiner requires Applicant to prove with 100% certainty that not a single contaminating bacterium is present anywhere in the process.

4. In order to meet the enablement requirements of 35 U.S.C. 112, first paragraph, the specification need only teach a person of ordinary skill in the art how to produce "a bacterium".

5. The Robinson and Steuer Declarations confirm and conclusively establish that the methods disclosed in the specification enable the production of a number of different kinds of bacteria.

6. The claimed methods do not lend themselves to producing any and all bacteria.

7. The claims do not recite methods producing specific bacteria, just any bacterium generally.

8. The claimed method does not require the isolation of the bacteria.

9. The Office has fundamentally misconstrued the nature of the invention.

10. The specification clearly states that the methods result in the acquisition by eukaryotic cells all of the morphological characteristics of prokaryotes and that the production of bacteria is not due to the presence of bacteria in the eukaryotic cell cultures.

11. Dr. Steuer states that persons skilled in the art do not apply the position taken by the Office.

12. The Declarations by Robinson and Steuer demonstrate that the claimed methods are completely repeatable.

13. The issues raised by the Office with regard to the viral and/or eukaryotic genes are not material to the claims since one of skill in the art would know that any gene present in the bacteria would be intact, stable and

integrated in the genome because that would be their condition prior to the performance of the claimed methods.

Examiner rebuts:

With regard to Point 1, all evidence of record has been fully considered. However, contrary to Applicant's assertion, said evidence does demonstrate enablement for the claimed invention. It should be noted that Applicant is being inconsistent in defining what constitutes the claimed invention. For instance, in Applicants traversal of the rejection made under 35 U.S.C. 101, defined the invention as a method that allows one to take cultured **retrovirally-infected** eukaryotic cells (uncontaminated with bacteria), subject them to a series of specific culturing conditions and obtain a culture of cells that **morphologically can only be described as bacteria** wherein said cells contain **intact** eukaryotic and/or viral genes (see page 8-9 of the appeal brief) whereas in his traversal of the instant rejection he defines the instant invention as a method to produce bacteria containing eukaryotic and/or viral genes from an aseptic culture of retrovirally-infected eukaryotic cells (see page 15 of appeal brief). Neither definition is accurate. All claims are drawn to the methods of producing bacteria containing a eukaryotic and/or viral gene not "cells that morphologically can only be described as bacteria wherein said cells contain intact eukaryotic and/or viral genes". Additionally, only claims 6-7, 11-12 and 18 recites the limitation that the eukaryotic cell has to be retrovirally infected. Furthermore, no claim recites the limitation that the eukaryotic or viral gene contained within the "produced" bacteria must be "intact". Finally, no claim recites the limitation that the eukaryotic cultures need to be "uncontaminated by bacteria" (i.e. be an aseptic culture).

With regard to Points 2-4, the rejection is not based on the belief that the bacteria "produced" is due to contamination of the starting cultures nor is the Office requiring Applicant to prove with 100% certainty that not

a single contaminating bacteria is present anywhere in the process. The instant rejection is based on the fact that the specification is enabling for the "isolation" of bacteria utilizing the claimed methods but not enabling for the "production" of bacteria using said methods. This point is supported by the fact that the claims of U.S. Patent 6,022,730 are drawn to methods of **isolating** a bacterium comprising aseptically culturing retrovirally transformed human capillary microvascular endothelial cells (ATCC CRL 11655); subjecting said culture to an anaerobic culturing phase wherein said culture is exposed to oxygen conditions corresponding to an atmosphere containing of about 0 to 2% v/v oxygen for a period of between 18 and 24 hours; exposing said culture to oxygen conditions corresponding to an atmosphere containing greater than 2% v/v oxygen; subjecting said culture to an additional anaerobic culturing phase wherein said culture is exposed to oxygen conditions corresponding to an atmosphere containing of about 0 to 2% v/v oxygen for a period of between 18 and 24 hours; subjecting said culture to an additional aerobic culturing phase under aseptic culturing conditions and corresponding to an atmosphere containing greater than about 2% v/v oxygen; isolating a bacterium from the culture (either *Staphylococcus aureus* ATCC 55589, *Staphylococcus capitis* ATCC 55590, *Staphylococcus hemolyticus* ATCC 55592, *Staphylococcus epidermidis* ATTC 55591 or *Micrococcm luteus* ATCC 55588). Which constitutes the full scope of enablement of the instant specification. Applicant is correct in his statement that in order to meet the enablement requirements of 35 U.S.C. 112, first paragraph, the specification need only teach a person of ordinary skill in the art how to produce "a bacterium" which possesses all the claimed limitations. The instant specification fails to meet this burden for the reasons outlined in the rejection.

With regard to Point 5, contrary to Applicant's assertion, the Robinson and Steuer Declarations do not conclusively establish that the methods disclosed in the specification enable the production of a number of different kinds of bacteria. In fact, the Steuer Declaration (and the Final Report on which it is based) discloses the **isolation** of a single known bacterial species from a single cell type (see page one of the Final Report).

Moreover, it should be noted that Dr. Steuer states in said report that the goal of the recited study was to "determine if bacteria **can be isolated** from cells maintained in anaerobic conditions..." (See page 2 of Final Report).

With regard to Points 6 and 7, the instant claims encompass any and all types of bacteria. Furthermore, it should be noted that Applicant has argued that the claimed methods are drawn to methods of producing altered cells that have all the morphological characteristics of bacteria (and hence would be classified as bacteria by the objective observer) from a culture of eukaryotic cells wherein said altered cells contain one or more eukaryotic or viral genes (see page 2 of the Appeal brief) **and** methods of producing bacteria from a culture of eukaryotic cells wherein said altered cells contain one or more eukaryotic or viral genes.

With regard to Point 8, claims 20-23 are specifically drawn to methods that further comprise filtering the cultured cells.

Contrary to Applicant's assertion the specification is not enabled for methods for **making, producing or generating** a bacterium that contains a eukaryotic and/or viral gene. As stated previously, the specification is only enabled for a method for **isolating** a bacterium comprising aseptically culturing retrovirally transformed human capillary microvascular endothelial cells (ATCC CRL 11655). The specification does not provide any mode of making and using the claimed invention throughout the scope of the claims. Contrary to the Applicant's assertion, the Declarations by Drs. Robinson (i.e. the Final Report) and Steuer do not establish that the methods disclosed in the instant application are enabled. In fact, Dr Steuer states (see page 1 of the final report) "reintroduction of an aerobic atmosphere during an anaerobic cell culture phase resulted in the **isolation** of bacteria, specifically *Bacillus lichenformis*". Additionally, the results presented by Dr Steuer were obtained using a single cell strain (RT-HMCV) and resulting in the **isolation** of a single known bacterial strain.

With regard to Point 9, Applicant states that the Office has fundamentally misconstrued the claimed invention. The claimed invention, as recited in the claims, is drawn to a method **of producing** a bacterium that contains a eukaryotic and/or viral gene wherein said method comprises culturing virally-infected eukaryotic cells under low oxygen conditions. Said method further comprises exposing said cells at least once to anaerobic or microaerophilic culture conditions. As stated before it does not appear that the claimed method would be suitable for the recovery of any and all bacteria regardless of if they were "produced" or merely the result of a contamination. From the record of the written disclosure specific bacteria were obtained by the cultivation of the specific cell lines in specific media. In view of the specific nutritional requirements of different types of "cell cultures" and of different bacteria, there is no reasonable expectation that any and all types of bacteria may be "produced" or even isolated from any and all cell cultures by the procedure claimed. For example, any anaerobic bacteria would be destroyed upon exposure to aerobic conditions. In addition, the claims lack specific method steps for the recovery of the bacteria. Thus, it is unclear that the claimed method would be suitable for the recovery of any and all bacteria, a few of which may be present, but not detectable by certain means.

With regard to Points 11 and 12, Applicant relies on the aforementioned Declarations as being demonstrative of the predictability and repeatability of the claimed methods. However, Dr. Steuer was only able to **isolate** a known bacterial species *(Bacillus licheniformis)* in half of his experiments and said bacterial species was different that disclosed in the specification even though the same starting materials and methods were used. Additionally, Dr. Steuer did not report the any cases of "de novo speciation". Therefore contrary to Applicant's assertion, it is apparent that the claimed method, minimally, is unpredictable and would appear to depend on the type of cell cultured and the type of virus employed. The specification is silent on the criteria employed in determining what cell culture to use in order to have a reasonable a degree of certainty that bacteria as required can be "produced", in the absence of positive steps to modify existing bacteria and to

assure the survival of the cell culture for a time period. Accordingly, in view of the lack of guidance, the claims as written constitute nothing more than an invitation to experiment.

The present invention would also require undue experimentation to practice in view of the unpredictable completion of the culturing steps. The specification indicates that the cultured cells under anaerobic conditions results in the death of the eukaryotic cells. However, the claims include no such limitation, accordingly, it is unclear if the eukaryotic cells are to be living or dead at this point. Likewise, the specification indicates that culturing under low oxygen conditions results in the production of the bacterium.

With regard to Point 13, contrary to Applicant's assertion, the issues raised by the Office with regard to the viral and/or eukaryotic genes are material to the claims since one of skill in the art would not know that any gene present in the bacteria would be intact, stable and integrated in the genome because that would be their condition prior to the performance of the claimed methods. Genes can exist extra-chromosomally (especially in bacteria) Therefore, one of the skill in the art would not know to determine whether a given viral and/or eukaryotic genes is an intact gene picked up rather than random fragment thereof. Additionally, the cell line the specification uses is a retrovirally-infected cell line. However, by convention, retroviral genes have been found to be ubiquitous in many different types of organisms, such that virtually any cell culture would reasonably be expected to have at least pieces of DNA from these viruses. Regarding the genes or fragments that are to be present in the bacteria, it is unclear whether such pieces are to be stably incorporated into the genome and whether proteins will be expressed.

Fourth Issue

Applicant argues:

1. The term "low oxygen conditions" would be readily understood by one of ordinary skill in the art in view of the definition of the term at page 9, lines 15-18.

2. Claims 2,3 and 15 are not confusing or contradictory in light of the definition of "low oxygen conditions".

3. With regard to Examiner's assertion that the term "a single eukaryotic gene" does not describe the instant invention, the specification makes clear that the genome of the bacteria produced need not comprise the complete genome of the starting eukaryotic cells (see page 7, lines 2-25). Additionally, the "viral and/or eukaryotic genes" might be altered. Also, each bacterium will contain at least one intact eukaryotic gene. Finally, the term the phrase "at least one eukaryotic gene" does not exclude an entire intact genome.

4. Claims 24 and 25 specifically reference claims 1 and 15, respectively. Therefore, the way the claimed cells are "derived" are expressly included in the claim.

5. The term "evolved" is well understood in the art to mean, "change over time". The clear meaning of the rejected claims is that the gene in the claimed cell has been changed from the gene of the starting eukaryotic cell by application of the process of either claim 1 or 15.

6. All cells are not "pleiomorphic" by nature. Moreover, the use of the term in the specification is in complete accordance with the accepted meaning. (e.g. page 29, lines 10-20). The Examiner's statement that "it is unclear how the cell of the instant claim differs from any other cell since all cells are pleiomorphic in nature" is baseless since these claims contain additional elements that distinguish the two cells and hence said distinction is not based only on the term "pleiomorphic".

7. There are certain morphologies that are well established as being characteristic of prokaryotic or eukaryotic cells. Moreover, when referring to the morphology of a cell, it is generally understood in the art that one is referring to the overall morphology unless specified otherwise. Thus the statement that the morphology of the cells is neither prokaryotic nor eukaryotic would be understood to mean that the overall morphology is not consistent with either. Any doubt as to the meaning of said phrase is removed by the disclosure (see page 29, lines 10-12; page 29, lines 21-22).

8. Although the specific words "not a transgenic cell" do not appear in the specification the specification as a whole reasonably conveys to a person having ordinary skill in the art that the instant method employs cells that are not transgenic and this is sufficient under the second paragraph of 35 U.S.C 112. The specification clearly states that an aspect of the method for producing bacterial cells expressing animal and/or viral genes does not require any step to introduce these genes into bacteria to create transgenic bacteria.

Examiner rebuts:

1. With regard to Point 1, contrary to Applicant's assertion, said term is not defined in the specification. The passage cited by Applicant states "suitable anaerobic conditions **include** an atmosphere of 0-2 v/v% oxygen". Since said statement merely identifies one of a multitude of possible concentrations, it is still impossible to determine the metes and bounds of the claimed invention. It should be noted that the upper limits of the claimed term encompass "microaerophilic" conditions.

2. With regard to Point 2, the rejected claims recite, "subjecting the cells to an aerobic culturing step", yet they depend (in the case of claims 2 and 3) upon claims that require culturing under low oxygen conditions. Applicant has previously argued that the two "steps" are delineated by the term "comprising" and hence are not confusing. However since no active steps are defined to separate the two steps they remain contradictory and confusing. It should also be noted that Applicant has previously acknowledged that the aforementioned rejection was warranted which is in itself contradictory to his stated traversal.

3. With regard to point 3, evidence that claims 1-29 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in Paper No. 7 and 8 filed 6-24-2000. In that paper, Applicant has stated "any eukaryotic genes present in bacteria produced by the claimed methods would be intact, stable and

integrated in the genome, because that would be their condition prior to the performance of the claimed methods", and this statement indicates that the invention is different from what is defined in the claim(s) because said statement indicates that the genome of the "produced" bacteria is eukaryotic in nature suggesting that the claimed method induces a "de-evolution" of the eukaryotic cell. The instant claims are drawn to methods of **producing a bacterium** that contains a single eukaryotic gene (which would have a prokaryotic genome) not a bacterium that has the phenotype of a prokaryote and the genotype of a eukaryote. It should be noted that Applicant has argued that the instant claims recite the limitation that the claimed bacteria will contain at least one eukaryotic gene. This limitation is not present in the instant claims. Said claims recite the limitation "bacterium containing a eukaryotic and/**or** viral gene.

4. With regard to Point 4: Contrary to Applicant's assertion, the way in which the claimed cells are "derived" is not expressly included in the claim since the independent claims (claims 1 and 15) recite open claim language. Consequently, it is unclear what constitutes a "derived" cell, how said cell differs from a "non-derived" cell or what steps are required for this "derivation".

5. The term "evolve" is defined as "To develop or arise through evolutionary processes". Said processes are gradual over time. Consequently, with regard to the instant claims, it is unclear what is meant by said term since all genes in a given eukaryotic genome have "evolved" from an ancestral genome since evolution is an inherent trait of all genomes. Moreover, it is unclear how the claimed "evolved" genes differ from their ancestral progenitors.

6. The term pleiomorphic is defined as "having the ability to change shape". Consequently, all cells are pleiomorphic since they have the ability to alter their shape based on environmental conditions etc. Moreover,

the presence of additional limitations within a claim does not lend "definiteness" to a given term. In the instant case, regardless of the additional limitations present in the claims, it is unclear how the cell of the instant claim differs from any other cell since all cells are pleiomorphic by nature.

7. Contrary to Applicant's assertion the rejected claims are rendered vague and indefinite by the use of the phrase "morphology that is neither prokaryotic nor eukaryotic". Contrary, to Applicants assertion, the cited passages of the specification are describing the shape (morphology) of the "bacteria" not the "overall morphology". No mention was made of the presence or organization of any internal organelles etc). Consequently, it is still not clear what is meant by said term or what morphology is included within the claimed limitations if eukaryotic and prokaryotic morphologies are excluded.

8. The term "transgenic" applies to any and all genes of the claimed bacteria not merely the eukaryotic and/or viral genes specifically recited in the claims. It should be noted that the instant rejection was made under 35 U.S.C 112, first paragraph, not 35 U.S.C. 112, second paragraph as stated by Applicant.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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